

Faulty Laboratory Results When to Suspect and How to Resolve

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Something Wrong?

- Case 1.
 - MTB tested S to all 1st-line drugs.
 - 3 months later, the culture tested R to all 1st-line drugs.
 - Acquired MDR?
- Case group 2 [Cases 2A & 2B].
 - Smears: all negative.
 - Culture: positive in 1 of 3
 - False or real positive?
- Case group 3 [Cases 3A, 3B & 3C].
 - A community hospital with low TB prevalence
 - 3 BAL specimens from 3 patients.
 - All three were smear-positive.
 - Real positive?

Case 1

- 52 yr Female immigrant.
- 1/13/05, PPD+, 15 mm, normal CXR
- 12/15/05, abnormal CXR, smear-, culture-
- 1/11/06, smear-, culture +,
 - S to all 1st line drugs (2/14/06).
- Treatment course was rough.
 - Could not tolerate drugs, stopped & reinstated 3 times.
 - Clinically worsened & continued to lose weight.
- 4/27/06, smear-, culture +,
 - R to all 1st line drugs.

Acquired MDR?

- Possible to acquire resistance to ALL 1st-line drugs in 3 months?
 - Yes? due to rough treatment course?
 - No?
- Primary MDR?
 - Initial drug results were wrong?!
 - How to prove it?
- Drug profile of the index case?
 - Not available.

Key Questions to ask

- Was SM tested in 1/06?
 - Yes. SM was S.
- Was patient treated with SM?
 - No!
 - How could SM become R?
- Initial drug results must be wrong!

When Did Error Occur?

- At specimen collection?
- When processing for smear & culture?
- When working up positive cultures?
- When testing drugs?
- When reporting results?

Investigation

- In the batch processed on 1/11/06,
 - Two specimens from two patients were culture-positive for MTBC.
- The two specimens were collected one day apart and checked in at different times.
 - no errors at check-in.
- At processing, the two specimens were next to each other.
 - Centrifuge tubes were labeled on top, not on tube.
 - Possible that two tubes were switched after centrifugation.
- Genotyping results (Spoligo & MIRU):
 - Case 1's 4/27/06 isolate (**Beijing**) did not match her 1/11/06 isolate **not Beijing**, a rare type.
 - The other patient's 12/05 isolate matched Case 1's 1/11/06 isolate—the same rare genotype.

What Could Have Been Done?

- If there was a doubt in initial drug results,
 - Discuss with lab.
 - Request repeat drug testing on another isolate, NOT on the same isolate.
 - Molecular beacon assay was requested, but the same “wrong” isolate was submitted. No mutations detected.
 - Did not help, just confirmed the wrong results.
- If patient’s clinical conditions were not improving, order lab tests sooner than 3 months.
 - Rapid MDR screening test .
 - Repeat DST.

False-positive?
or
True-positive?

False or True Positive?

- Smears—all 3 negative; Cultures—only 1 of 3 positive.
 - False-positive
 - The rate varies. Median: 3.1% (2.2%-10.5%).
 - Ref: Burman. Clin Infect Dis, 2000; 31:1390
 - Possible causes: contamination of clinical devices, clerical errors, lab cross-contamination, etc.
 - True-positive
 - Low organism load.
 - Very slow-growing strains—can be drug-resistant TB!
 - Poor specimen quality.
 - Poor collection, storage, or transport condition, etc.

Investigate to Get CORRECT Results

- Very critical.
- Assuming either false or true positive may lead to wrong diagnosis.
- Interaction with lab will help investigation.

Group 2—Cases 2A & 2B

Which Case Is A Real Positive?

Case 2A

- A 55 yr old female, coughing for months,
- 3 sputa for AFB, mycology and routine bacteriology.
- Smears: negative,
- Cultures: 1/3 positive by BACTEC 460 at 5 weeks, and 1 rough colony on 7H10. MTBC identified.

Case 2B

- A 28 yr old male immigrant, asymptomatic.
- At immigration screening, 3 sputa collected for AFB.
- Smears: negative,
- Cultures: 1/3 positive by MGIT 960 at 3 weeks. MTBC identified.

Suggestions for Investigation

- More than 1 positive specimen in the batch?
- Error-prone techniques?
 - Inadequate labeling? Not checking labels? Not opening one tube at a time? Adding reagents from a common vessel?
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- Mishandling positive cultures?
- Reporting errors?
- If suspected, genotyping may help to confirm.



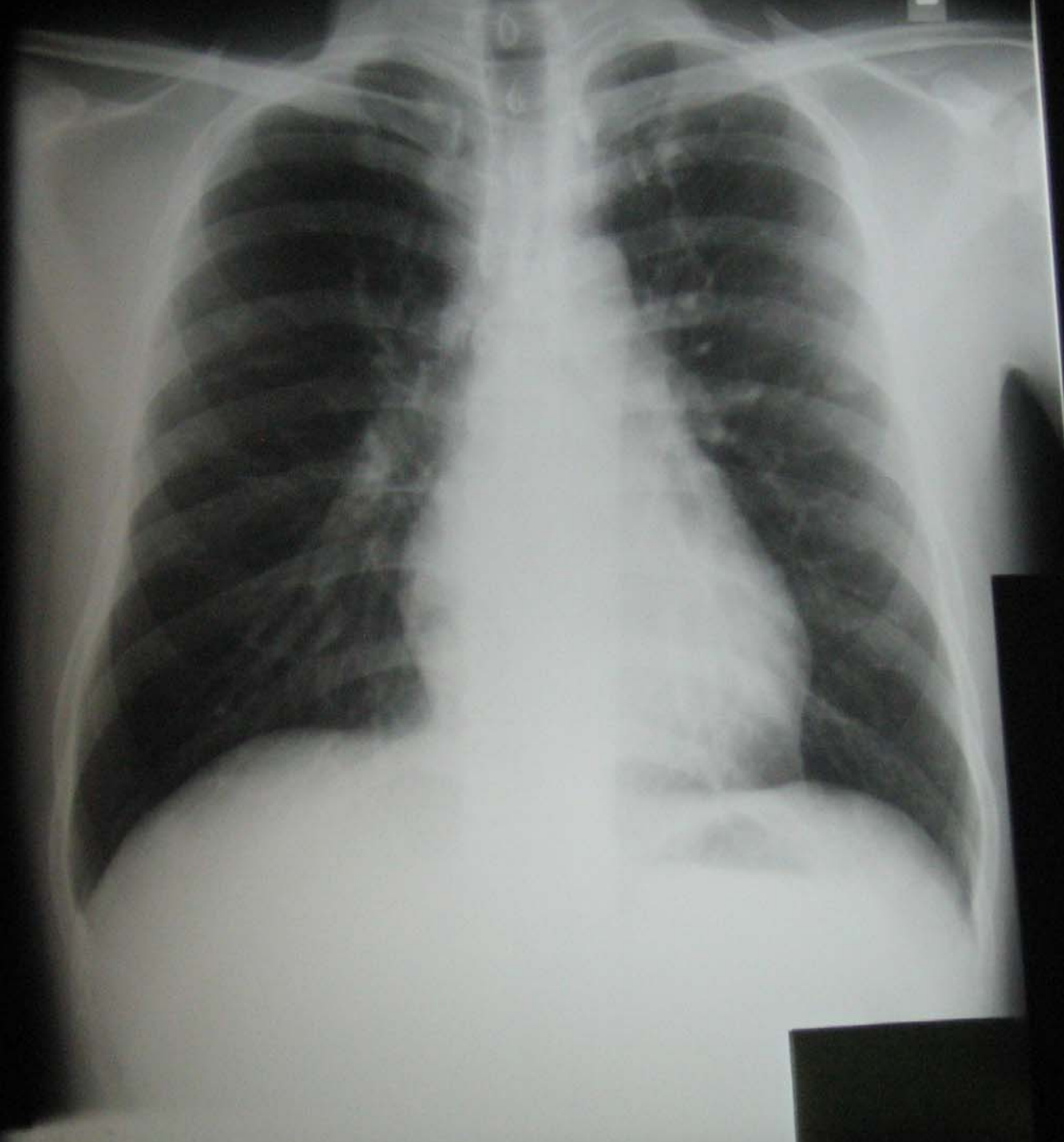
Case 2A

Investigation

- More than one positive culture in the batch.
- Case 2A's specimen processed after a specimen with numerous AFB.
- The culture became positive at 5 week.
 - Unusually delayed.
- Possible cross-contamination?
 - Yes, possible, if the lab does not use good techniques, & does not have a good quality system in place.
- Variables to consider:
 - Clinical findings?
 - Request for genotyping to prove it.
 - Test additional good quality specimens if necessary.

Case 2B

- 28 yr old male immigrant, asymptomatic.
- Treated for TB with standard regimen from 7/05 to 1/06 before coming to USA.
- 6 months later, at immigration screening, CXR was slightly abnormal (see CXR).
- 3 smears: negative; cultures: pending.



Case 2B

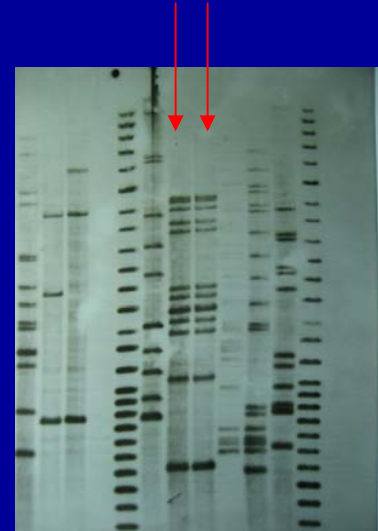
- Patient moved to another state.
- Subsequent 3 specimens:
 - smear-negative and culture-pending.
- CA: 1/3 culture positive
 - Molecular beacon: MDR.
- **Are you convinced this was a real MDR TB?**
- Patient was put on observation, not treated for MDR TB, because
 - CXR: not really abnormal.
 - Positive MTB result: possible false-positive.

Case 2B

Investigation

- No other specimens yielded positive cultures in the batch.
- When patient 2B's culture turned positive, no other cultures did on the same day.
- The lab used MGIT 960, a closed system
 - does not introduce cross-contamination.

Final Answers



- Case 2A:
 - Lung cancer.
 - Proven to be a “Cross-contamination”.
 - RFLP had the same pattern as the index case.
- Case 2B:
 - The positive culture was real.
 - No sources of cross-contamination found.
 - MDR TB.
 - MB detected mutations & DST showed R to SIREP.
 - Confirmed by additional lab tests. [more to follow]

Case 2B (part II)

- Patient returned to CA in 11/06.
- CXR slightly worsened.
- 3 more specimens obtained:
 - Smears: negative, only 1 culture grew MTB.
- Culture grew very slowly.
 - MB testing requested on 2/16/07.
 - MDR! Previous results were confirmed.
- DST: R to SIREP & S to LV, ETA, AK & CM.
- MDR regimen started in 2/07.
 - Treatment was delayed for 6 months due to doubts in initial results.

Case Group 3 [3A, 3B, 3C]

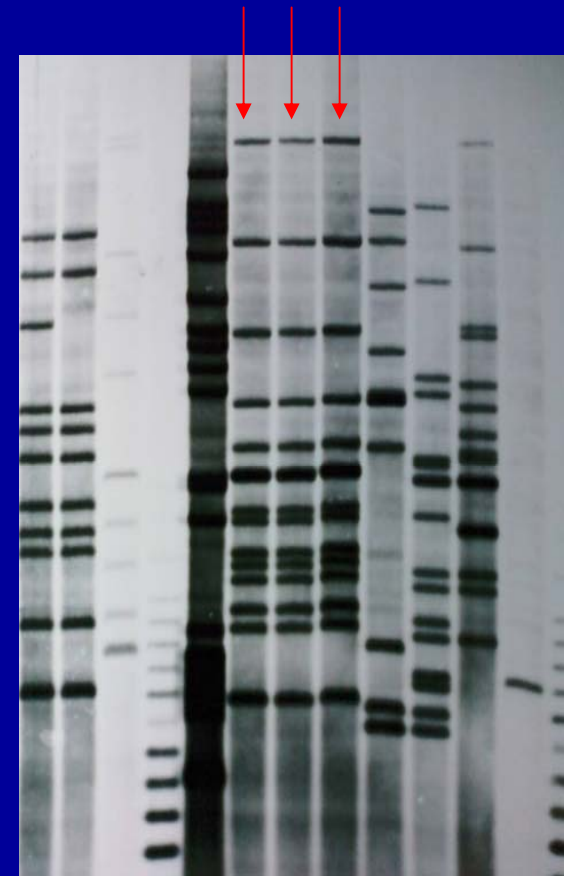
- A regional laboratory noticed AFB smear was positive on:
 - 3 BAL specimens
 - from 3 different patients
 - in 3 consecutive days
 - from a community hospital where TB prevalence was low.

Actions from Lab

- Suspicions of something wrong on 3rd day:
 - This hospital has a low smear-positive rate
 - Only BAL, not other specimen types.
 - Case 3A: many AFB
 - Subsequent cases 3B & 3C: rare AFB.
- Lab called the Respiratory unit:
 - asked to check if positive AFB results were compatible with patients' clinical manifestations.

Where was the Error from?

- Not from lab!
- Contaminated bronchoscope!!
 - Inadequate sterilization.
 - Manufacturer had to implement a new sterilization procedure.
- Confirmed by RFLP
 - Identical pattern.

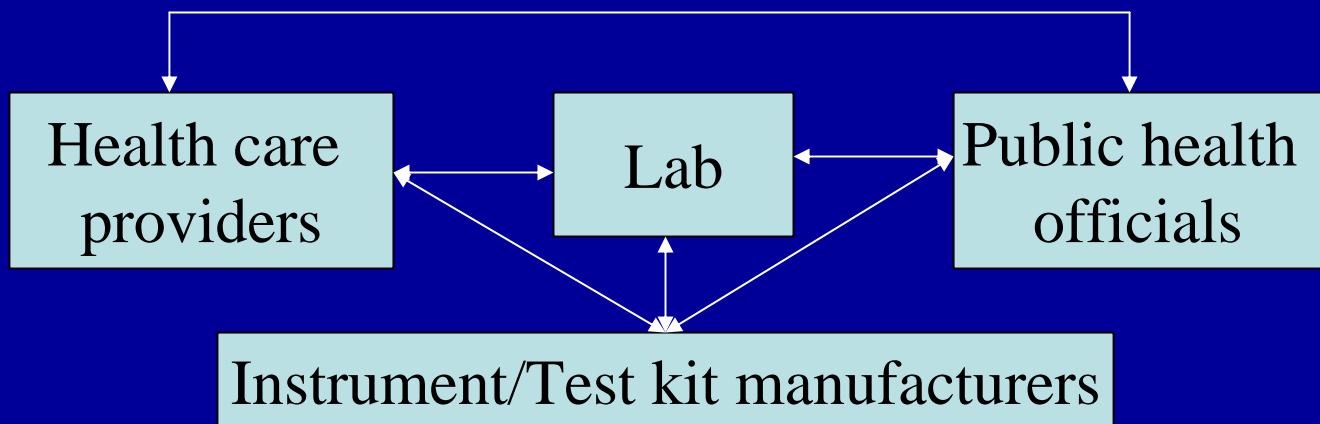


Summary: Sources of Error

- Pre-analytical
 - Improper collection, storage, transport, labeling, etc.
 - Cross-contamination
 - Medical procedures, medical devices
- Analytical
 - Technical errors in setting up cultures, working up positive cultures, performing drug susceptibility testing, etc.
 - Test kits problem (misabeled by manufacturer, inadequate validation, etc.)
 - Cross Contamination
 - During processing cultures
 - Lab instruments
- Post-analytical
 - Errors in data entry, etc.
- Others

Communication!!

- Be alert when something seems “unusual”.
- Multi-channel Communication:



- Build relationships and trust through candid discussion and mutual education.

Conclusions

- Direct communication between health care providers and labs is critical to resolve errors.
- Resolving errors through thorough investigation
 - discover sources of error.
 - implement corrective actions to prevent recurrences.
- Lab is a strong ally with other health care providers and TB control programs in the battle ground of fighting TB.

Questions?